Journal of the American College of Cardiology
© 2001 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 37, No. 3, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(00)01189-X

The Repolarization-Excitability Relationship in the Human Right Atrium Is Unaffected by Cycle Length, Recording Site and Prior Arrhythmias

Frank Bode, MD,*† Michael Kilborn, MD,* Pamela Karasik, MD, FACC,*
Michael R. Franz, MD, PHD, FACC*
Washington, DC

OBJECTIVES The goal of this study was to determine the relationship between repolarization and excitability in the human atrium under various conditions.

BACKGROUND Action potential duration (APD) measurements from monophasic action potential (MAP) recordings provide a surrogate for measuring the effective refractory period (ERP) in human ventricle. The relationship between repolarization and refractoriness in human atrium and the effect of prior atrial fibrillation/flutter on the ERP/APD correlation are unknown.

METHODS Seven patients with sinus rhythm and 15 patients after conversion of atrial flutter or fibrillation were evaluated. Monophasic action potentials were recorded at multiple right atrial sites and during different basic cycle lengths from 300 to 700 ms, while ERPs were determined by extrastimulus technique using the MAP recording-pacing combination catheter.

RESULTS There was a close correlation between ERP and APD at 70% repolarization (APD_{70}, $r = 0.97$; $p < 0.001$) and 90% repolarization (APD_{90}, $r = 0.98$; $p < 0.001$), respectively. Refractoriness occurred at a repolarization level of 72 ± 8%. The ERP/APD_{70} and ERP/APD_{90} ratios averaged 1.06 ± 0.10 and 0.86 ± 0.08, respectively. These ratios were nearly constant over the entire range of basic cycle lengths, between different sites in individual patients and between different patients. Patients cardioverted from atrial fibrillation or flutter exhibited no significant differences in the ERP/APD relationship compared with patients with sinus rhythm.

CONCLUSIONS Effective refractory period and APD are closely related in the human right atrium. Using the MAP recording technique, atrial ERPs can be assessed by measurement of APDs. Effective refractory period is most closely reflected by APD_{70}. Thus, MAP recordings allow investigation of the local activation and repolarization time course beat by beat, visualizing the excitable gap. (J Am Coll Cardiol 2001;37:920–5) © 2001 by the American College of Cardiology

Myocardial cells regain excitability as repolarization progresses—in both a voltage-dependent and time-dependent manner (1). Therefore, a relatively close relationship can be expected to exist between the duration of repolarization (or the action potential duration [APD]) and the duration of the effective refractory period (ERP). Previous in vitro studies using microelectrode technique (2,3) and in vivo studies using the monophasic action potential (MAP) recording technique (4,5) have shown that, in ventricular myocardium, ERP ends when the action potential repolarizes to the 75% to 85% level (6–9). Myocardial disease or antiarrhythmic drug treatment (primarily with sodium-channel blocking agents) may change this relationship by causing postrepolarization refractoriness (3,4,8,10). Yet, under normal conditions, ventricular APD can be regarded as a surrogate for ERP.

In atrial myocardium, the relationship between ERP and APD has not been sufficiently evaluated. Little is known about the direct relationship of atrial ERP and APD at different cycle lengths (11), and no data exist for the human in situ heart.

This study set out to determine the relationship between APD and ERP in the human atrial myocardium in vivo. Our study was prompted by the following considerations. If a similar correspondence and stability of the ERP/APD ratio could be found in the atrium, as was previously established for the ventricle, several purposes would be served: 1) Atrial ERPs could be assessed directly by measuring atrial APDs (using the MAP technique) during atrial electrophysiological interrogations; 2) these assessments would be valid at any given spontaneous or paced cycle length or recording site; 3) APD, rather than ERP, measurements would suffice to determine the spatial and temporal dispersion of atrial refractoriness without the need for interrupting the prevailing cycle length by repeated extrastimuli, which are bound to perturb the steady state; and 4) it would allow the distinction between the approximate end of refractoriness and the following depolarization during spontaneous atrial tachyarrhythmias, thus allowing the electrophysiologist direct visualization of the excitable gap (12,13).

METHODS

Patients. Measurements were performed in 22 patients (21 men and 1 woman) aged 24 to 80 years (mean 65 ± 13). Seven patients underwent routine electrophysiological stud-

From the *Veteran Affairs Medical Center and Georgetown University, Washington, DC; and †Medizinische Klinik II, Universitaetsklinikum, Luebeck, Germany.

Manuscript received December 3, 1999; revised manuscript received October 6, 2000, accepted November 17, 2000.

Abbreviations and Acronyms

APD = action potential duration
APD_{70} = action potential duration at 70% repolarization
APD_{90} = action potential duration at 90% repolarization
ERP = effective refractory period
MAP = monophasic action potential

ies for evaluation of syncope or nonsustained ventricular tachycardia. Twelve patients were studied 10 min after cardioversion of atrial fibrillation (n = 6) or flutter (n = 6). Three patients were investigated 30 min after atrial flutter ablation. Demographic and clinical data of the patient population are summarized in Table 1. All patients gave written informed consent to the protocol that had been approved by the institutional ethics review board. Antiarrhythmic drugs had been discontinued for at least 5 half-lives before the study.

Electrophysiological study. A monophasic action potential recording/pacing combination catheter (6) (EP Technologies Inc., San Jose, California) was introduced via a femoral vein and positioned in the right atrium. The catheter position was documented by fluoroscopy in right anterior oblique and left anterior oblique projection. Monophasic action potentials and surface electrocardiogram leads were recorded on a BARD computer system. Pacing and MAP recording were performed simultaneously at the same endocardial site. Continuous overdrive pacing at 2× diastolic threshold strength and a basic drive cycle length of 600 ms was performed for 2 min before each recording to establish steady state. After a train of eight stimuli (S_1), an extrastimulus (S_2) was introduced during the diastolic interval. With each train, the S_1-S_2 coupling interval was decreased in steps of 5 ms until the ERP was reached, defined by the longest S_1-S_2 interval that failed to induce a propagated response (Fig. 1). The pause between drive trains was 2 s.

Table 1. Selected Clinical and Electrophysiologic Features of Study Patients*

	Age (yrs)	Arrhythmia Diagnosis	LA Size (mm)	LVEF (%)	Afib/flut Duration (months)	Conversion Mode
			Control Patients			
	77	syncope	42	67		
	49	nsVT	39	30		
	65	syncope	37	60		
	24	syncope	30	58		
	73	nsVT	47	40		
	55	syncope	41	73		
	80	syncope	45	45		
Mean	60.4		40.1	53.3		
SD	19.7		5.6	15.4		
			Patients With Aflut			
	78	typical	40	50	2	DC shock
	52	typical	52	30	N/A	pace out
	67	typical	43	55	0.75	DC shock
	64	atypical	44	55	18	pace out
	74	typical	48	50	1.5	pace out
	80	typical	43	35	2	pace out
	64	typical	42	35	20	ablation
	77	atypical	45	45	1	ablation
	51	typical	45	20	7	ablation
Mean	67.4		44.7	41.7	7.4	
SD	10.8		3.5	12.2	8.2	
			Patients With Afib			
	67		59	55	5	DC shock
	58		48	35	28	DC shock
	74		51	55	0.75	DC shock
	77		49	60	26	DC shock
	65		48	25	2	DC shock
	62		41	55	1	DC shock
Mean	67.2		49.3	47.5	10.5	
SD	7.2		5.8	14.1	12.9	

*Mean age, LA size and LVEF were not significantly different between groups.

Afib = atrial fibrillation; Aflut = atrial flutter; DC = direct current; LA = left atrial; LVEF = left ventricular ejection fraction; N/A = not applicable; nsVT = nonsignificant ventricular tachycardia; pace out = termination of atrial flutter by overdrive pacing.

To determine whether the relation between repolarization and refractoriness varies between different atrial sites, the catheter was repositioned to at least one other right atrial site in each patient, and the protocol was repeated. Recordings were obtained from the high right atrium, anterior/appendage locations, midseptal and posterior sites, lateral free wall and low right atrium.

In nine patients, extrastimulation was performed at basic cycle lengths of 700 ms, 600 ms, 500 ms, 400 ms and 300 ms at the same atrial site to investigate the effect of cycle length changes on the ERP/APD relation.

Data analysis. The following variables were analyzed: 1) MAP duration at 70% repolarization (APD_{70}) and 2) at 90% repolarization (APD_{90}), 3) ERP and 4) the repolarization level at which refractoriness occurred (Fig. 1). The ratios between ERP and APD_{70} and between ERP and APD_{90} were calculated.

Statistics. Data are presented as mean ± standard deviation. Two-way analysis of variance for mixed effects was used to test differences in ERP, APD and ERP/APD ratios between various sites and cycle lengths with post hoc analysis by Bonferroni. Sites or cycle lengths contributed fixed effects, while single patients contributed random effects. Group dependent differences were evaluated by one-way repeated-measures analysis of variance using a mixed model. Correlations between ERP and APD were evaluated by linear regression analysis. A $p < 0.05$ defined statistical significance.

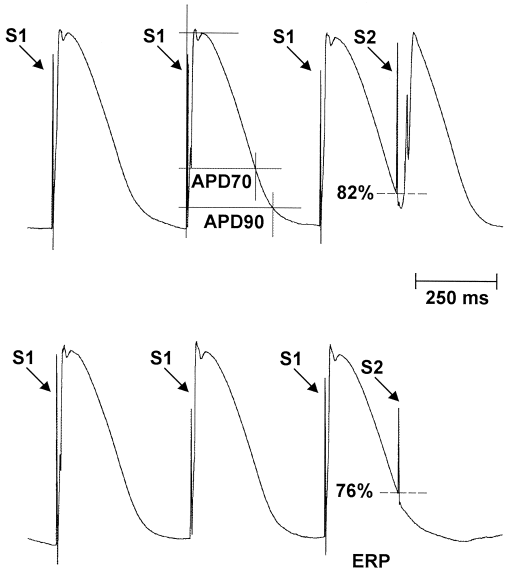

Figure 1. Simultaneous measurement of effective refractory period (ERP) and action potential duration at 70% repolarization (APD_{70}) and 90% repolarization (APD_{90}) with the combination catheter. S_1 and S_2 denote the basic and extrastimulus artifacts. Repolarization levels (n%) at which extrastimuli are superimposed onto the preceding repolarization phase are visualized.

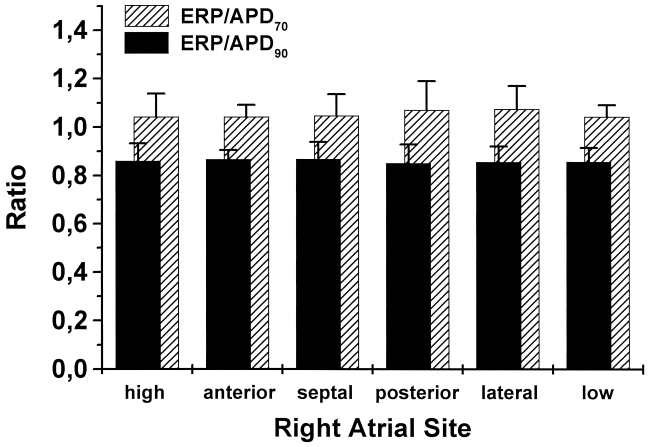

Figure 2. Ratio between effective refractory period (ERP) and action potential duration at 70% (APD_{70}) and 90% repolarization (APD_{90}) at different right atrial sites. Ratios exhibited no significant site-specific differences.

RESULTS

Stable MAP recordings were obtained in all patients. The average diastolic pacing threshold through the MAP combination catheter was 0.4 ± 0.2 mA.

ERP/APD ratio at different sites. At a basic cycle length of 600 ms, APD and ERP were determined at two to six different sites in each patient (average 2.8 sites). A large dispersion of APD_{90} was found between similar atrial locations in different patients (80 ± 12 ms) and between different atrial sites in an individual patient (39 ± 18 ms). The dispersion of ERP averaged 59 ± 13 ms between similar locations in different patients and 34 ± 17 ms between different atrial sites in an individual patient. Despite this dispersion, there was a close relation between APD and ERP because the intra- and interindividual repolarization levels at which refractoriness occurred were fairly identical. On average, the ERP occurred at 72 ± 9% repolarization of the preceding action potential. The relationship between APD and ERP is commonly expressed by the ERP/APD ratio. The overall ERP/APD_{90} ratio was 0.86 ± 0.08; the overall ERP/APD_{70} ratio was 1.06 ± 0.10. The ERP/APD ratios showed no appreciable difference between various right atrial sites (Fig. 2).

ERP/APD ratio at different steady-state cycle lengths. A decrease in basic cycle length from 700 ms to 300 ms shortened APD_{90} from 285 ± 26 ms to 232 ± 23 ms ($p < 0.001$) and APD_{70} from 233 ± 19 ms to 188 ± 19 ms ($p < 0.001$). In parallel, ERP shortened from 247 ± 20 ms to 197 ± 20 ms ($p < 0.001$). Linear regression analysis of 12 paired recordings at different right atrial sites and different basic cycle lengths in nine patients revealed that APD and ERP were highly correlated ($r = 0.85$ both for APD_{90} and APD_{70}; $p < 0.001$, Fig. 3). When recordings from a single site were evaluated over different basic cycle lengths, the correlation between APD and ERP was even more stringent (average correlation of paired data sets: $r = 0.98$ for APD_{90}; $p < 0.001$ and $r = 0.97$ for APD_{70}; $p < 0.001$). Conse-

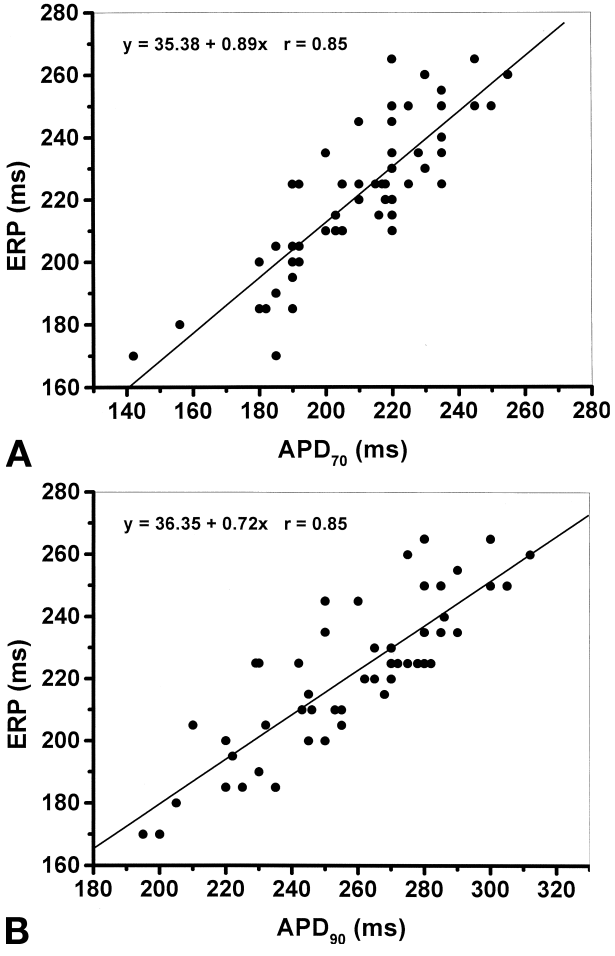

Figure 3. (A) Correlation between effective refractory period (ERP) and action potential duration at 70% repolarization (APD_{70}) and **(B)** between ERP and action potential duration at 90% repolarization (APD_{90}). Measurements were obtained at 12 different right atrial sites and different steady state cycle lengths in nine patients.

quently, the ERP/APD_{90} and ERP/APD_{70} ratios remained nearly constant during a stepwise decrease in cycle length (Fig. 4).

ERP/APD ratio in patients with prior atrial fibrillation or flutter. Patients cardioverted from atrial fibrillation or atrial flutter tended to have slightly shorter APD and ERP than control patients despite the same paced cycle length. The ERP/APD ratios, however, did not differ between patient groups, indicating that the repolarization level at which refractoriness occurred was not influenced by the prior existence of an atrial arrhythmia (Table 2).

DISCUSSION

This study shows a close relationship between repolarization and refractoriness in the human right atrium. The relationship was found to be highly constant between different atrial sites and over a wide range of atrial cycle lengths. It was not influenced by a prior atrial arrhythmia.

Unlike conventional clinical pacing and recording techniques, the MAP recording/pacing catheter allowed stimulation and recording at nearby myocardial sites. Due to the short distance (<2 mm) between the distal pacing electrode pair and the proximal recording electrode pair, local electrical responses could be obtained with a minimum of distant electrical activity. Stimulus artifacts were minimized by low stimulus thresholds and did not interfere with simultaneously recorded action potentials (6,14,15). The repolarization time course could, therefore, be analyzed precisely in the immediate vicinity of the pacing site.

Atrial ERP/APD ratio. Compared with action potentials recorded from ventricular myocardium, atrial action potentials are more triangular in shape because of a shorter phase 2 and a decreased slope of phase 3 (14,16). In the human ventricle, refractoriness occurs at approximately 85% repolarization with stimuli of twice diastolic threshold strength (5); while in the atrium, it occurred at approximately 72% repolarization. Regardless of these differences, which might be explained by different ion current distributions in atrial and ventricular cells, our study confirmed the close correlation of APD and ERP in the right atrium that has previously been demonstrated in ventricular myocardium using microelectrode (2,3) or MAP recording techniques (7,8). Action potential durations at 90% and 70% repolarization were similarly correlated to the ERP, showing that both indexes of the repolarization time course can be employed to express the relationship between repolarization and refractoriness in the human right atrium. Because refractoriness was found to occur at about 72% repolarization, APD_{70} reflected the ERP more closely than APD_{90}. Therefore, APD_{70} appears to be the more accurate index for estimation of the right atrial ERP in drug-free myocardium. Antiarrythmic drugs, especially class I, may change the ERP/APD ratio to higher values, as was previously shown for the human ventricle (3,4,8,10).

Site independence of the ERP/APD ratio. Our study found a considerable dispersion of repolarization and refractoriness between various atrial sites at a fixed cycle length. Substantial site to site differences in APD and ERP are

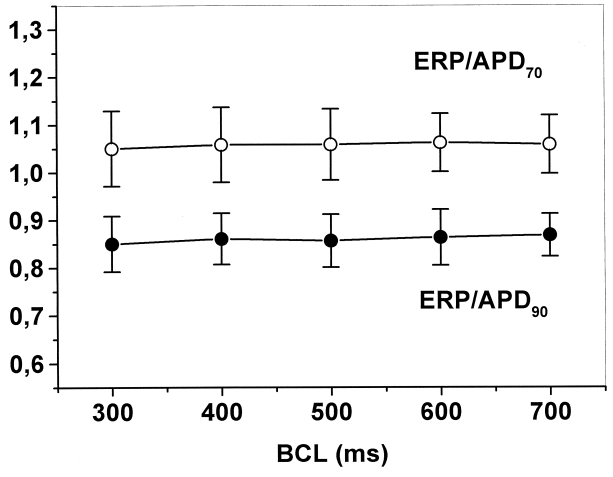

Figure 4. Ratio between effective refractory period (ERP) and action potential duration at 70% (APD_{70}) and 90% repolarization (APD_{90}) as a function of basic cycle length (BCL). Ratios showed no significant cycle length-dependent changes.

Table 2. Right Atrial Repolarization and Refractoriness at Identical BCL in Control Patients, Patients With Aflut and Afib

Patients	BCL (ms)	APD_{70} (ms)	APD_{90} (ms)	ERP (ms)	Repol. (%)	ERP/APD_{70}	ERP/APD_{90}
Control (n = 7)	600	223 ± 33	274 ± 43	234 ± 29	72 ± 10	1.06 ± 0.12	0.86 ± 0.08
Aflut (n = 9)	600	218 ± 20	266 ± 25	230 ± 20	72 ± 9	1.06 ± 0.09	0.87 ± 0.06
Afib (n = 6)	600	209 ± 33	257 ± 39	219 ± 10	73 ± 10	1.07 ± 0.12	0.87 ± 0.09

Afib = Atrial fibrillation; Aflut = atrial flutter; APD_{70} = Action potential duration at 70% repolarization; APD_{90} = action potential duration at 90% repolarization; BCL = basic cycle length; ERP = effective refractory period; Repol. = repolarization level at which refractoriness occurred.
p = n.s. for intergroup differences.

known to occur even between adjacent myocardial locations (17–20). Possible mechanisms underlying nonuniform repolarization and refractoriness between different myocardial areas are inhomogeneous distribution of ion channels and cardiac "memory" (21–23). However, these intersite differences in atrial repolarization did not lead to appreciable changes in the average atrial ERP/APD ratio between sites, indicating that changes in local refractoriness are always closely related to repolarization despite site-specific variations in APD. The correlation between APD and ERP was highly significant for different myocardial sites and even more stringent at a single site. The difference might be explained by slightly different action potential configurations between sites, particularly the phase 3 repolarization time course. Action potentials might be more triangular at one site and more dome-shaped at another site, which can create certain variations in the calculated ERP/APD ratios between sites. At a given site, the slope of phase 3 and, consequently, the ERP/APD ratio were constant, even if APD changed during adaptation to a new cycle length.

Cycle-length independence of the ERP/APD ratio. In ventricular myocardium, changes in APD due to alterations in cycle length are paralleled by concurrent changes in ERP (7–9). Our study confirmed at the atrial level that the cycle length dependence of repolarization and refractoriness, likewise, are closely interrelated. For the same slope-related reasons (see previous text), the average ERP/APD ratio for different atrial cycle lengths shows a standard deviation that is explained by small intersite differences in the ERP/APD ratio rather than cycle-length dependent variations in the ratio at a given site.

Implications. The MAP recordings of the atrial repolarization time course allow the clinical investigator to estimate local refractoriness over a wide range of atrial rates. This might be particularly helpful during sudden rate changes where refractory period determinations are impractical, yet MAP recordings display the repolarization time course on a beat-to-beat basis. Therefore, estimations of atrial refractoriness by MAP recordings are feasible even in the presence of continuous cycle length changes due to atrial arrhythmias.

The atria of patients with atrial fibrillation or flutter have been shown to undergo persistent electrophysiological changes due to the presence of the arrhythmia, termed electrical remodeling (24). A shortening of ERP (25) and APD (26) and a loss of physiological rate adaptation of the APD was noted, particularly at longer cycle lengths (26). This study found small differences in APD and ERP between control patients and patients cardioverted from atrial fibrillation or flutter but no significant differences in the ERP/APD relationship. This suggests that atrial remodeling does not affect the close relation between myocardial repolarization and refractoriness, allowing accurate estimation of local refractoriness by MAP recording in patients with prior atrial tachyarrhythmias. As was already suggested by previous studies, MAP recordings may allow continuous monitoring of APD and estimation of ERP even during atrial fibrillation or flutter, thereby allowing one to directly visualize the excitable gap between repolarization and the subsequent depolarization (12,13).

Conclusions. For the human right atrium, we documented a close correlation between repolarization and the recovery of excitability, with no significant effects on this relationship by cycle length, recording site or prior tachyarrhythmias. These first in vivo data of the human atrial ERP/APD relationship provide validation of using APD measurements from MAP recordings as a surrogate for ERP determinations.

Reprint requests and correspondence: Dr. Michael R. Franz, Cardiology Division, Veteran Affairs Medical Center, 50 Irving St., NW, Washington, DC 20422. E-mail: mfranz@washington.va.gov.

REFERENCES

1. Luo CH, Rudy Y. A model of the ventricular cardiac action potential. Depolarization, repolarization and their interaction. Circ Res 1991;68:1501–26.
2. Davidenko JM, Antzelevitch C. Electrophysiological mechanisms underlying rate-dependent changes of refractoriness in normal and segmentally depressed canine Purkinje fibers: the characteristics of postrepolarization refractoriness. Circ Res 1986;58:257–68.
3. Nattel S, Zeng FD. Frequency-dependent effects of antiarrhythmic drugs on action potential duration and refractoriness of canine cardiac Purkinje fibers. J Pharmacol Exp Ther 1984;229:283–91.
4. Franz MR, Costard A. Frequency-dependent effects of quinidine on the relationship between action potential duration and refractoriness in the canine heart in situ. Circulation 1988;77:1177–84.
5. Koller BS, Karasik PE, Solomon AJ, Franz MR. Relation between repolarization and refractoriness during programmed electrical stimulation in the human right ventricle: implications for ventricular tachycardia induction. Circulation 1995;91:2378–84.

6. Franz MR, Chin MC, Sharkey HR, Griffin JC, Scheinman MM. A new single-catheter technique for simultaneous measurement of action potential duration and refractory period in vivo. J Am Coll Cardiol 1990;16:878–86.
7. Bargheer K, Bode F, Klein HU, Trappe HJ, Franz MR, Lichtlen PR. Prolongation of monophasic action potential duration and the refractory period in the human heart by tedisamil, a new potassium-blocking agent. Eur Heart J 1994;15:1409–14.
8. Lee RJ, Liem LB, Cohen TJ, Franz MR. Relation between repolarization and refractoriness in the human ventricle: cycle length dependence and effect of procainamide. J Am Coll Cardiol 1992;19:614–8.
9. Sager PT, Nademanee K, Antimisiaris M, et al. Antiarrhythmic effects of selective prolongation of refractoriness: electrophysiologic actions of sematilide HCl in humans. Circulation 1993;88:1072–82.
10. Costard-Jaeckle A, Liem LB, Franz MR. Frequency-dependent effect of quinidine, mexiletine and their combination on postrepolarization refractoriness in vivo. J Cardiovasc Pharmacol 1989;14:810–7.
11. Boutjdir M, Le Heuzey JY, Lavergne T, et al. Inhomogeneity of cellular refractoriness in human atrium: factor of arrhythmia? Pacing Clin Electrophysiol 1986;9:1095–100.
12. Stambler BS, Wood MA, Ellenbogen KA. Pharmacologic alterations in human type I atrial flutter cycle length and monophasic action potential duration. Evidence of a fully excitable gap in the reentrant circuit. J Am Coll Cardiol 1996;27:453–61.
13. Franz MR. Atrial fibrillation and atrial flutter seen through the "eye" of monophasic action potential recordings. In: Saoundi N, Schoels W, (N.) El-Sherif, editors. Atrial Flutter and Fibrillation: From Basic to Clinical Applications. Armonk, NY: Futura Publishing, 1998:177–91.
14. Franz MR. Long-term recording of monophasic action potentials from human endocardium. Am J Cardiol 1983;51:1629–34.
15. Franz MR, Burkhoff D, Spurgeon H, Weisfeldt ML, Lakatta EG. In vitro validation of a new cardiac catheter technique for recording monophasic action potentials. Eur Heart J 1986;7:34–41.
16. Hoffman BF, Cranefield PF. Electrophysiology of the Heart. Mount Kisko, NY: Futura Press, 1960.
17. Franz MR, Bargheer K, Rafflenbeul W, Haverich A, Lichtlen PR. Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence for the genesis of the T wave. Circulation 1987;75:379–86.
18. Vassallo JA, Cassidy DM, Kindwall KE, Marchlinski FE, Josephson ME. Nonuniform recovery of excitability in the left ventricle. Circulation 1988;78:1365–72.
19. Cowan JC, Hilton CJ, Griffiths CJ, et al. Sequence of epicardial repolarization and configuration of the T wave. Br Heart J 1988;60:424–33.
20. Autenrieth G, Surawicz B, Kuo CS. Sequence of repolarization on the ventricular surface in the dog. Am Heart J 1975;89:463–9.
21. Rosenbaum MB, Blanco HH, Elizari MV, Lazzari JO, Davidenko JM. Electrotonic modulation of the T wave and cardiac memory. Am J Cardiol 1982;50:213–22.
22. Costard-Jackle A, Goetsch B, Antz M, Franz MR. Slow and long-lasting modulation of myocardial repolarization produced by ectopic activation in isolated rabbit hearts: evidence for cardiac "memory." Circulation 1989;80:1412–20.
23. Shvilkin A, Danilo P, Jr., Wang J, et al. Evolution and resolution of long-term cardiac memory. Circulation 1998;97:1810–7.
24. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. Circulation 1995;92:1954–68.
25. Cosio FG, Palacios J, Vidal JM, Cocina EG, Gomez-Sanchez MA, Tamargo L. Electrophysiologic studies in atrial fibrillation: slow conduction of premature impulses: a possible manifestation of the background for reentry. Am J Cardiol 1983;51:122–30.
26. Franz MR, Karasik PL, Li C, Moubarak J, Chavez M. Electrical remodeling of the human atrium: similar effects in patients with chronic atrial fibrillation and atrial flutter. J Am Coll Cardiol 1997;30:1785–92.